disclosure rules in Part 20 of this chapter.

(Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704))

Effective date: This regulation is effective September 30, 1982.

Dated: August 9, 1982.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Richard S. Schweiker,

Secretary of Health and Human Services.

[FR Doc. 82-23777 Filed 8-30-82; 8:45 am]

BILLING CODE 4160-01-M

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21 CFR Part 331

[Docket No. 78N-0433]

Antacid Drug Products for Over-the-Counter Human Use; Labeling

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: This document amends the labeling provisions for over-the-counter (OTC) antacid drug products to permit the use of the term "upset stomach." The Food and Drug Administration (FDA) is taking this action because it has concluded that consumers use the term "upset stomach" to describe symptoms associated with gastric hyperacidity. In addition, FDA is amending the monograph for OTC antacid drug products to include a "Statement of Identity" paragraph. The agency is taking this action after considering public comments on the proposed rule. This final rule is part of FDA's ongoing review of OTC drug products.

EFFECTIVE DATE: The effective date of the regulation is September 30, 1982. OTC antacid drug products complying with the labeling proposed in the September 21, 1979 proposal may continue to be introduced into interstate commerce until August 31, 1983.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, National Center for Drugs and Biologics (HFD–510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of September 21, 1979 (44 FR 54731), FDA proposed to amend the antacid monograph (21 CFR Part 331) to permit OTC antacid drug products to be labeled for the relief of upset stomach associated with heartburn, sour stomach, and acid indigestion. The agency also proposed to amend § 331.30 (21 CFR 331.30) to include a "Statement of Identity" paragraph to conform with the format of other recently proposed OTC drug monographs.

Interested persons were invited to file written comments regarding this proposal on or before November 20, 1979. In response to the proposed rule, comments were received from three manufacturers and one trade association.

This final rule contains the agency's decision to amend the labeling requirements for OTC antacid drug products to permit antacid drug products to be labeled for relief of upset stomach associated with heartburn, sour stomach, and acid indigestion, and to amend § 331.30 to include a "Statement of Identity" paragraph.

A. The Agency's Conclusions on the Comments

1. Several comments agreed with the agency's proposal to permit OTC antacids to be labeled "for the relief of upset stomach associated with heartburn, sour stomach, and/or acid indigestion." One comment added that the proposed amendment would make the approved indications more comprehensible to consumers.

2. A comment contended that OTC monographs issued under the OTC drug review process are interpretive, as opposed to substantive, regulations. The comment referred to previous comments regarding this issue, dated March 4, 1972, on the Proposed Procedural Regulations Governing the OTC Review, and comments dated June 4, 1973, on the Proposed Antacid Monograph.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464), and in paragraph 3 of the preamble to the tentative final order for antacid products, published in the **Federal Register** of November 12, 1973 (38 FR 31260), and FDA reaffirms the conclusions stated there. Subsequent court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F. 2d 688, 696–98 (2d Cir. 1975); *National Association of Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F. 2d 887 (2d Cir. 1981).

3. One comment argued that labeling terminology which is truthful, accurate, nonmisleading, and intelligible to the consumer may not legally be prohibited by the promulgation of OTC drug monographs purporting to contain exclusive lists from which OTC labeling pertaining to indications for use must be drawn. The comment also incorporated by reference similar comments submitted on November 22, 1978, on the Proposed Establishment of a Monograph for OTC Sunscreen Drug Products.

Since the inception of the OTC drug review, the agency has maintained that a monograph describing the conditions under which an OTC drug will be generally recognized as safe and effective and not misbranded must include both specific active ingredients and specific labeling. (This policy has become known as the "exclusivity rule.") The agency's position has been that it is necessary to limit the acceptable labeling language to that developed and approved through the OTC drug review process in order to ensure the proper and safe use of OTC drugs. The agency has never contended, however, that any list of terms developed during the course of the review literally exhausts all the possibilities of terms that appropriately can be used in OTC drug labeling. Suggestions for additional terms or for other labeling changes may be submitted as comments to proposed or tentative final monographs within the specified time periods or, as in the case of the present document, through petitions to amend monographs under 21 CFR 330.10(a)(12).

During the course of the review, FDA's position on the "exclusivity rule" has been questioned many times in comments and objections filed in response to particular proceedings and in correspondence with the agency. The agency has also been asked by The Proprietary Association to reconsider its position. To assist the agency in resolving this issue, FDA plans to conduct an open public forum on September 29, 1982 where all interested parties can present their views. The forum will be a legislative type administrative hearing under 21 CFR Part 15 that will be held in response to a request for a hearing on the tentative final monograph for nighttime sleep-aids (published in the **Federal Register** of June 13, 1978; 43 FR 25544). Details of the hearing were announced in a notice published in the **Federal Register** of July 2, 1982 (47 FR 29002). In proposed, tentative final, and final monographs (including amendments to final monographs) that are issued in the meantime, the agency will continue to state its longstanding policy.

4. A comment stated that proposed § 331.30(b) (1) and (2) could be interpreted to require literal repetition of the terms "heartburn," "acid indigestion," and/or "sour stomach" when used in connection with the term

"upset stomach," even if those terms are also used alone. As an example, the comment suggested alternative labeling such as "For the relief of heartburn, acid indigestion, sour stomach, and upset stomach associated with these symptoms." Another comment noted that many OTC antacids are marketed in rolls, where label space is already at a minimum. The comment requested that the proposed rule be revised in order to abbreviate the indications statement, and proposed the following labeling: "For relief of (optional, any or all of the following) heartburn, sour stomach, acid indigestion, and/or associated upset stomach."

The agency agrees that the indications statement as proposed in § 331.30(b) could be repetitious and thus require more label space than is necessary to convey the intended information. Accordingly, proposed § 331.30(b) is revised as follows:

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following: "For the relief of" (optional, any or all of the following:) "heartburn," "sour stomach," and/or "acid indigestion" (which may be followed by the optional statement:) "and upset stomach associated with" (optional, as appropriate) "this symptom" or "these symptoms."

5. A comment stated that the data used by FDA in making the determination that the upset stomach indication could be allowed also demonstrate that consumers do use words other than those specifically defined by the OTC Antacid Panel to describe symptoms that can be relieved by antacids. The comment argued that these data provide a basis upon which FDA could reasonably adopt the position that words of similar meaning to the consumer can be used in addition to those words specifically defined by the OTC panels as indications for OTC drug products. Accordingly, the comment requested that the following additional indications for OTC antacids be accepted by FDA and be incorporated into the monograph on the basis that they are similar and not meaningfully different to the consumer than those labeling indications currently allowed:

a. "Stomach pain associated with (acid indigestion, heartburn, and/or sour stomach)";

b. "Stomach ache associated with (acid indigestion, heartburn, and/or sour stomach)";

c. "Stomach distress associated with (acid indigestion, heartburn, and/or sour stomach)";

d. "Gastric upset associated with (acid indigestion, heartburn, and/or sour stomach)";

e. "Queasy stomach associated with (acid indigestion, heartburn, and/or sour stomach)";

f. "Nausea associated with (acid indigestion, heartburn, and/or sour stomach)."

The agency notes that the comment submitted no additional data to support its position. As indicated in the Warner-Lambert Co. and the Miles Laboratories, Inc., petitions (discussed in the preamble to the September 21, 1979 proposal), and as accepted by the agency, the term "upset stomach" is a general term used by consumers to describe clusters of symptoms. Frequently, specific symptoms of hyperacidity such as acid indigestion, heartburn, or sour stomach are included among the symptoms by which consumers describe their "upset stomach." By proposing this phrase in antacid labeling, the agency intended the "associated with" language to inform the consumer that the antacid is effective for "upset stomach" insofar as specific symptoms of hyperacidity such as acid indigestion, heartburn, or sour stomach are part of that cluster of symptoms. FDA is not convinced that antacid drug products are effective in relieving all the specific symptoms of what a consumer might describe generally as an upset stomach. On this basis, the agency considers that three of the terms the comment proposes for inclusion in the monograph (stomach pain, stomach ache, and nausea) are specific terms that relate to distinct and definable conditions, separate from the cluster of symptoms that a consumer may associate with the relief of hyperacidity (acid indigestion, heartburn, and/or sour stomach). In addition, the terms "stomach pain" and "stomach ache" imply that the drug provides an analgesic effect, i.e., relieves pain, and antacids do not have this pharmacologic action. The agency believes that two of the terms ("stomach distress" and "gastric upset") may denote to some people a cluster of symptoms associated with allowable antacid indications, but it does not believe that these terms are used frequently enough by a sufficient number of consumers to be accurate and meaningful to consumers generally. In fact, none of the subjects in the studies described in either the Warner-Lambert Co. or the Miles Laboratories, Inc., petitions even specifically mentioned either term. In addition, the agency placed the terms "nausea" and "stomach distress" in Category II and antacid claims. (See the **Federal Register** notice of September 5, 1978 (43 FR 39427).) The final term ("queasy stomach") proposed by the comment denotes a group of symptoms somewhat similar to upset stomach, but it is a term also closely associated with the term "nausea." The agency notes that, in the Warner-Lambert Co. petition, the term "queasy stomach" was included with terms used to describe nausea and, in this context, may be closely associated with a specific definable condition. The agency believes that the terms "queasy stomach" and "nausea" may be more appropriately addressed in the rulemaking for OTC antiemetic drug products. Moreover, on page 54732 of the September 21, 1979 proposal the agency referred the review of ingredients for the relief of gastrointestinal distress from causes other than gastric hyperacidity to the Advisory Review Panel on OTC Miscellaneous Internal Drug Products. For the reasons explained above, the agency has determined that none of the six terms requested by the comment may be included in the antacid monograph.

6. A comment stated that the Miles Laboratories, Inc., and the Warner-Lambert Co. data, which the agency used to establish that consumers use one or more of the three approved antacid claims ("heartburn," "sour stomach," or "acid indigestion") to describe their "upset stomach," also clearly indicate that consumers use the term "nausea" to describe their "upset stomach." The comment argued that, based on the evidence reviewed by FDA and the fact that the agency has accepted the use of the "upset stomach associated with * * *" claims for antacid drug products, FDA must act consistently and recognize the claim for "upset stomach associated with nausea (and queasiness)" in related rulemaking proceedings, particularly in the antiemetic drug products final monograph.

The comment has not requested any specific action regarding the antacid final monograph (21 CFR Part 331). The agency is reviewing and will address the comment's request for an "upset stomach associated with nausea (and queasiness)" claim in the Antiemetic Drug Products Final Order (21 CFR Part 336), which will be published in a future issue of the **Federal Register.**

7. A comment stated that manufacturers should be permitted to submit data to the Miscellaneous Internal Panel in support of those claims which may be included in the upset stomach syndrome, but which do not

clearly fall within the purview of the antacid or antiemetic drug monographs.

Manufacturers have had an opportunity to submit such data to the Miscellaneous Internal Panel. In the September 21, 1979 proposal (44 FR 54731) to amend the antacid monograph to permit the "upset stomach" claim, the agency noted that terms such as "heartburn" may also be used by consumers to describe gastrointestinal distress resulting from other causes, such as overindulgence in food and drink. As the agency stated in the proposal (44 FR 54731), the review of ingredients for the relief of gastrointestinal distress from causes other than gastric hyperacidity was referred to the Miscellaneous Internal Panel. That Panel's review included the data in the Miles Laboratories, Inc., petition and other data. Accordingly, the agency will defer its decision regarding the use of the "upset stomach" claim for categories of OTC drug products under review by the Miscellaneous Internal Panel until that Panel's conclusions are published in the **Federal Register.**

8. A comment stated that "the manner in which FDA is proceeding on the upset stomach claims * * * is confusing and * * * the agency (should) clarify its position in the final order on this proposal." The comment went on to argue that FDA "must address the pending reviews of the other components of the upset stomach claim for antiemetic drug products and other digestive relief products scheduled for review by the Miscellaneous Internal Drug Products Panel." The comment cited case law and a **Federal Register** notice concerning the use of descriptive phrases in antacid labeling in support of its position that the other "upset stomach associated with * * *" claims must be addressed under this final order.

The agency has explained in previous responses to comments how the upset stomach claim will be dealt with in the relevant rulemaking proceedings. The comment raises issues about claims that are not proposed for use under the antacid monograph. Although unnecessary, a response to the arguments made in the comment follows.

The **Federal Register** notice cited by the comment did not permit manufacturers to include new indications for use in antacid labeling. Instead, it allowed the use of descriptive phrases or adjectives, such as "sparkling," which had no bearing on the therapeutic action or effect of the antacid. The document is thus irrelevant to a rule permitting an additional therapeutic labeling claim.

The comment also contended that "as a matter of law, FDA's decision to permit the immediate use of the indication 'upset stomach associated with heartburn, sour stomach, acid indigestion,' can only mean that FDA views the action to be nonsubstantial." The comment cited the case of *American College of Neuropsychopharmacology* v. *FDA* (No. 75–1187, D.D.C., 1975) as support for this position. That case is not applicable to the "upset stomach" proposed rule. The case held that FDA could not publish certain procedural regulations as a final rule without first proposing them. Here, the agency has proceeded by way of a proposal to amend the OTC antacid monograph. That FDA allowed the use of the upset stomach indication prior to amendment of the final monograph was the product of the agency's policy of allowing Category I labeling recommended in a panel report or tentative final monograph to be used prior to promulgation of a final monograph, subject to the possibility that FDA may change the labeling as a result of new data or comments filed in response to the proposal or tentative final monograph. This policy is justified by FDA's belief that such labeling changes are beneficial to the consumer and does not signify a judgement that such actions are "nonsubstantial."

As justification for its position that "the use of the term 'upset stomach' associated with other subsets of the * * * syndrome must be specifically permitted in the (antiemetic) final order, pending appropriate review," the comment relied on *Rhodia, Inc., Hess & Clark Division* v. *FDA*, 608 F. 2d 1376 (D. C. Cir. 1979). The cited case states that, once FDA channels its discretion in a certain manner, it must follow a consistent course or articulate reasons for departing from it. FDA agrees with that principle and is applying it here by considering whether to permit the term "upset stomach" associated with other components of the upset stomach syndrome in the antiemetic and miscellaneous internal drug rulemaking proceedings. In the antacid proceeding, antacids have not been shown to relieve components of the upset stomach syndrome other than those for which labeling has been specified in the antacid monograph.

B. The Agency's Final Conclusions on OTC Labeling of Antacid Drug Products

Based on the available evidence and the comments received by the agency during the comment period, the agency is amending the OTC antacid monograph to permit antacids to be labeled "for the relief of" (optional, any or all of the following:) "heartburn," "sour stomach," and/or "acid indigestion" (which may be followed by the optional statement:) "and upset stomach associated with" (optional, as appropriate) "this symptom," or "these symptoms."

In the September 21, 1979 proposal the agency stated that manufacturers of OTC antacid drug products may adopt the proposed labeling as of the date of publication of the proposal, subject to the possibility that the FDA may change its position or alter the wording of the claim as a result of comments filed in response to the proposal. As noted above, the agency has changed the wording of § 331.30(b). Because FDA allowed the proposed claim to be used, the agency advises that such labeling may continue to be used after the date of publication of this final rule. The agency concludes that manufacturers can, within a 12-month period ending on August 31, 1983, use up existing labeling that complies with the September 21, 1979 proposal. After August 31, 1983, any OTC antacid drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

The agency received no comments in regard to the proposal to amend § 331.30 to include a "Statement of Identity" paragraph that conforms with the format of other recently proposed OTC drug monographs. Therefore, § 331.30 is amended to incorporate the proposed paragraph.

The agency has examined the economic consequences of this rulemaking and has determined that it does not require a Regulatory Impact Analysis as specified in Executive Order 12291. The final rule allows manufacturers the option to expand the labeling previously identifed in the OTC antacid drug products final monograph (21 CFR Part 331). If manufacturers choose not to exercise the option, this rule would have no effect. If manufacturers choose to exercise the option and expand the labeling of OTC antacid drug products, this rule would not precipitate any immediate effects; i.e., stocks of existing labeling could be used until manufacturers determine an appropriate time for relabeling. In addition, according to the September 21, 1979 proposal, the agency stated that manufacturers of OTC antacid drug products could adopt the proposed labeling subject to the possibility that FDA may change its position or alter the wording of the proposed labeling in the final rule. For manufacturers who did not adopt the proposed labeling, this

rule has no effect. For manufacturers who adopted the proposed labeling, FDA advises that these manufacturers may continue to use existing labeling for a period of 12 months after the date of publication of this final rule. Therefore the agency concludes that the final rule is not a "major" rule as defined in section 1(b) of Executive Order 12291. The requirement for a regulatory flexibility analysis under the Regulatory Flexibility Act does not apply to this final rule because the proposed rule was issued prior to January 1, 1981, and is therefore exempt.

List of Subjects in Part 331

OTC drugs, Antacids.

PART 331—ANTACID DRUG PRODUCTS FOR OVER-THE-COUNTER (OTC) HUMAN USE

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701m 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21U.S.C. 321(p), 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)) and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), Part 331 of Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations is amended in § 331.30 by revising paragraph (a); redesignating existing paragraphs (b), (c), (d), and (e) as (c), (d), (e), and (f), respectively; and adding new paragraph (b) to read as follows:

§ 331.30 Labeling of antacid products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antacid."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following: "For the relief of" (optional, any or all of the following:) "heartburn," "sour stomach," and/or "acid indigestion" (which may be followed by the optional statement:) "and upset stomach associated with" (optional, as appropriate) "this symptom" or "these symptoms."

* * * * *

Effective date: This regulation is effective September 30, 1982.

(Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended) (5 U.S.C. 553, 554, 702, 703, 704))

Dated: August 9, 1982.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Richard S. Schweiker,

Secretary of Health and Human Services.

[FR Doc. 82-23776 Filed 8-30-82; 8:45 am]

BILLING CODE 4160-01-M